Associations of dietary diversity score, obesity, and high-sensitivity C-reactive protein with HbA1c

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Abstract

Background: Associations of dietary diversity score (DDS), obesity and high-sensitivity C-reactive protein (hs-CRP) with glucose metabolism have been reported. Furthermore, DDS may not be associated with healthy weight. However, studies on these topics are limited in general Indonesia population. **Methods**: A total of 3,825 Indonesia Family Life Survey 2014/2015 participants aged 20–59 years old were included in this study. DDS was measured qualitatively in five food groups: carbohydrates, proteins, dairy products, vegetables, and fruits. Obesity was defined by Body Mass Index (BMI) classification for Indonesians. Blood analyses were performed in dried blood spot specimens. hs-CRP were analyzed using enzyme-linked immunosorbent assay and HbA1c was analyzed using Bio-Rad D10. **Results**: High DDS group had higher HbA1c than low DDS group ($p = 0.030$). Furthermore, medium and high DDS group had higher BMI than low DDS group ($p = 0.003$ and <0.001). Obese group had higher HbA1c than nonobese group ($p < 0.001$). hs-CRP was correlated with HbA1c ($r = 0.1194$; $p < 0.001$). Multivariate analysis showed that DDS, obesity and hs-CRP were associated with HbA1c ($p = 0.030$, $p < 0.001$ and <0.001). **Conclusions**: Present study confirmed that obesity and hs-CRP are associated with HbA1c. DDS is positively associated with HbA1c and BMI. Promoting dietary diversity requires careful consideration. Moreover, further studies are warranted.

Keywords: C-reactive protein, diet, HbA1c, obesity

Introduction

HbA1c has been widely used as a glucose control marker and is considered the best indicator for long-term glycemic control in diabetic patients because it reflects average blood glucose levels over 2–3 month period of time.[1] The use of HbA1c for the diagnosis of diabetes has also been suggested. HbA1c of 6.5% is recommended cut-off point for the diabetes diagnosis by American Diabetes Association[2] and World Health Organization.[3] In addition, HbA1c measurement offers some advantages compared with fasting blood glucose and 2-hour postprandial glucose irrespective of fasting, decreased biologic variability and unaffected by acute changes in blood glucose.[4]

It has been accomplished that HbA1c is a useful screening tool for blood glucose abnormalities and diabetes in population.[5] Studies reported that HbA1c is a strong predictor for diabetes[6] and is associated with higher risk for diabetes.[7] HbA1c has also been found to be associated with cardiovascular disease[8] and all-cause mortality in people without diabetes.[9]

Dietary diversity is one component of healthy diet which has been recommended in Indonesia nutrition guidelines.[10] It has been reported that dietary diversity and variety is inversely associated with diabetes in both cross-sectional[11] and prospective study.[12] Dietary Diversity Score (DDS) is a scoring system to measure the diversity food consumed at the household or individual level at daily, weekly or monthly basis.[13] DDS is negatively associated with various components of the metabolic syndrome including glucose abnormalities, hypercholesterolaemia, hypertension, and high low-density lipoprotein cholesterol.[14]

However, DDS may not be associated with healthy diet to promote healthy weight. A systematic review reported that DDS was not associated with body mass index status.[15] On the other hand, evidence also noted that greater dietary diversity may be associated with suboptimal eating pattern and weight gain in population.[16] Greater DDS was found to be associated with higher energy intake. Thus, DDS may not a good index to evaluate the healthfulness of the diet especially in obesity control.[17]

Evidence showed that obesity is associated with glucose abnormality and is one of the major risk factors for diabetes.[18] Obesity is associated with blood glucose abnormalities including type 2 diabetes mellitus, impaired glucose tolerance and impaired fasting glucose.[19] Consequently, it is recommended for overweight and obese people to perform blood glucose screening for risk of diabetes and cardiovascular disease.[5]

High-sensitivity C-reactive protein (hs-CRP) is a more sensitive measure of CRP that can detect very low CRP concentrations with sufficient precision.[20] Constant findings suggested that CRP is associated with glucose homeostasis. CRP is positively associated with metabolic syndrome,[21] prediabetes,[22] and diabetes mellitus.[23] Study also reported that hs-CRP can predict the occurrence of diabetes.[23]

There has been growing evidence that dietary diversity, obesity, and hs-CRP are associated with glucose metabolism. Moreover, there are controversies in the literature that dietary diversity may not be associated with healthy diet to promote healthy weight. However, studies on the association between obesity and HbA1c as well as their potential interrelationships with dietary diversity score and hs-CRP are limited in the general Indonesian population. Therefore, the objective of this study was to determine the association between HbA1c and obesity as well as their potential interrelationships with dietary diversity score and hs-CRP in Indonesian adults.

Methods

Study design. We conducted a cross-sectional study of 3,859 Indonesian adults from the Indonesia Family Life Survey 2014/2015. The Indonesia Family Life Survey (IFLS) is a continuing longitudinal survey in Indonesia. The first survey (IFLS1) was initiated in 1993 and the most recent survey (IFLS5) was conducted in 2014/2015. IFLS1 sampled households from 13 provinces in Indonesia using stratified random sampling and collected data on individual, household and community level. The resulting sample of IFLS1 represented approximately 83% of the Indonesia population in 1993. IFLS5 sampled original households and split-off households from IFLS1. A total of 50,148 individuals from 16,204 households were interviewed in IFLS5. Complete details about IFLS are described elsewhere.[24] IFLS5 data are open to public use and available for download after registration in RAND Corporation website (http://www.rand.org/labor/FLS/IFLS/ifls5.html).

Participants included in this study were 20–59 years old and had HbA1c, hs-CRP, anthropometric (height and weight) and food consumption data. Participants were excluded if they were diagnosed with tuberculosis, asthma, arthritis/rheumatism, liver diseases, kidney diseases, heart problems, stroke, cancer or malignant tumors.

Blood biochemical analyses. Dried blood spot (DBS) specimens were used in blood biochemical analysis. The analysis has followed validated protocols and quality control studies. Bio-Rad D10 high-pressure liquid chromatography (HPLC) was used in HbA1c assay. CRP was measured using high-sensitivity CRP (hs-CRP) enzyme-linked immunosorbent assay (ELISA) method. Description about IFLS blood sampling and analysis is available elsewhere.[25]

Dietary Diversity Score (DDS). DDS was measured qualitatively in five major food groups consumed by the subjects over the last 7 days, which were: (1) carbohydrate sources; (2) proteins; (3) milk and dairy products; (4) vegetables; and (5) fruits. The major groups then were divided into 10 subgroups according to the Food and Agriculture Organization (FAO) classification. Subgroups distribution was also based on food item listed in questionnaire. These subgroups are (1) grains (rice); (2) tubers (cassava); (3) meat (beef, chicken, pork, etc.); (4) eggs; (5) fish; (6) dairy products; (7) vitamin A rich vegetables (carrot); (8) green leafy vegetables; (9) vitamin A rich fruits (mango and papaya); and (10) other fruit (banana). Consumption of each food subgroup was scored 1 if consumed at least once in 7 days and scored 0 if not consumed at all. Scores of all food subgroups were summed so that the maximum possible score was 10. DDS was then categorized into low ($\leq$3), medium (4–5) and high ($\geq$6).[13]

Anthropometry measurements. Measurements followed standard procedure. Camry model EB1003 Scale was used to measure weight and Seca plastic height board model 213 was used to measure height. All measurements were only performed once. Obesity was then defined using the body mass index classification for Indonesians (BMI > 27).[10]

Data analyses. Analyses were performed using Stata Statistical Software Release 13 (StataCorp LP, College Station, Texas, USA). Data were described in frequency distribution, mean ± standard deviation or median and 25th–75th percentiles. Data of hs-CRP were log-transformed for bivariate and multivariate analysis because they are not normally distributed. Before data was transformed into logs, each hs-CRP value was augmented by one because many observations had hs-CRP value lower than the measurement lowest detection point.[26,27] Person's correlation coefficient was used to analyze the correlation between two variables. Student's t-test or ANOVA with Tukey's post hoc test were used to compare mean between or among groups. Multiple linear regression was used in multivariate analysis. Statistical significance was indicated by $p < 0.05$.

Ethics approval. This study was approved by Medical and Health Research Ethics Committee, Faculty of Medicine Universitas Gadjah Mada (Ref:KE/FK/0523/

EC/2018). IFLS surveys were approved by Institutional Review Boards at RAND Corporation in the United States and Survey Meter in Indonesia. All IFLS5 participants gave written inform consent.

Results

This study included 3,825 participants (2,101 women and 1,724 men). A total of 62.61% participants were under 40 years old. In this study, 32.89% of participants were smokers. The proportion of obese subjects was 20.13%. A total of 65.15% of subjects were in the high food diversity group, 27.27% were in the medium food diversity group, and 7.58% were in the low food diversity group. The mean of HbA1c was 5.54±1%. Median (25th–75th percentiles) of hs-CRP was 0.78 mg/L (0.29–2.23 mg/L) (Table 1).

There was difference in mean of HbA1c across DDS group (p = 0.030). There was an increase in HbA1c along with an increase in the DDS group and the high DDS group had significantly higher HbA1c levels than the low DDS group. Obese group had higher mean HbA1c than the nonobese group ($p < 0.001$). Differences in mean of HbA1c were detected across the hs-CRP groups where hs-CRP of 1–3 mg/L; >3–10 mg/L; >10 mg/L had higher HbA1c than those with <1 mg/L (Table 2). In addition, correlation test showed that hs-CRP was positively correlated with HbA1c ($p < 0.001$) (Figure 1).

Table 1. Characteristics of participants

Variables	n (%)		
	Female (n = 2,101)	Male (n = 1,724)	Total (n = 3,825)
Age			
20–39 years	1,280 (60.92)	1,115 (64.68)	2,395 (62.61)
40–59 years	821 (39.08)	609 (35.32)	1,430 (37.39)
Education			
No education	91 (4.33)	27 (1.57)	118 (3.08)
Elementary school	664 (31.60)	450 (26.10)	1,114 (29.12)
Secondary school	415 (19.75)	320 (18.56)	735 (19.22)
High school	591 (28.13)	658 (38.17)	1,249 (32.65)
Higher education	340 (16.18)	269 (15.60)	609 (15.92)
Settlement region			
Urban	1,222 (58.16)	1,027 (59.57)	2,249 (58,80)
Rural	879 (41.84)	697 (40.43)	1,576 (41,20)
BMI			
Underweight	153 (7.28)	231 (13.40)	384 (10.04)
Normal	1,052 (50.07)	1,079 (62.59)	2,131 (55.71)
Overweight	346 (16.47)	194 (11.25)	540 (14.12)
Obese	550 (26.18)	220 (12.76)	770 (20.13)
Dietary Diversity Score			
Low	149 (7.09)	141 (8.18)	290 (7.58)
Medium	573 (27.27)	470 (27.26)	1,043 (27.27)
High	1,379 (65.64)	1,113 (64.56)	2,492 (65.15)
HbA1c			
<5.7%	1,496 (71.20)	1,123 (65.14)	2,619 (68.47)
5.7≤6.5%	448 (21.32)	498 (28.89)	946 (24.73)
≥6.5%	157 (7.47)	103 (5.97)	260 (6.80)
hs-CRP			
<1 mg/L	1,047 (49.83)	1,110 (64.39)	2,157 (56.39)
1–3 mg/L	564 (26.84)	393 (22.80)	957 (25.02)
>3–10 mg/L	403 (19.18)	170 (9.86)	573 (14.98)
>10 mg/L	87 (4.14)	51 (2.96)	138 (3.61)
Smoking			
No	2,053 (97.72)	514 (29.81)	2,567 (67.11)
Yes	48 (2.28)	1,210 (70.19)	1,258 (32.89)
Medication			
Anemia	88 (4.19)	17 (0.99)	105 (2.75)
Hypertension	48 (2.28)	17 (0.99)	65 (1.70)
Diabetes	25 (1.19)	10 (0.58)	35 (0.92)
Cholesterol	13 (0.62)	19 (1.10)	32 (0.84)
HbA1c[*]	5.51±1.06	5.57±0.92	5.54±1
hs-CRP[#]	1.01 (0.35–2.78)	0.58 (0.23–1.55)	0.78 (0.29–2.23)

*data in mean ± standard deviation; #data in median (25th–75th percentiles)
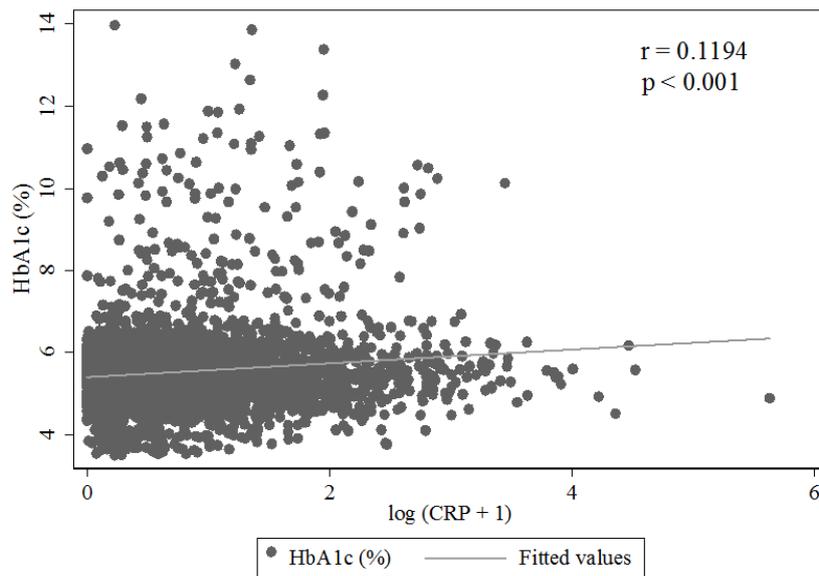
Figure 1. Correlation of log (hs-CRP + 1) and HbA1c

Table 2. Mean HbA1c according to participants' characteristics

Variables	Mean ± SD	SEM	95% CI	p
Sex				
Female	5.51 ± 1.06	0.02	5.46–5.55	0.050
Male	5.57 ± 0.92	0.02	5.53–5.61	
Age				
20–39	5.39 ± 0.85	0.02	5.36–5.44	<0.001
40–59	5.78 ± 1.17	0.03	5.72–5.84	
Diet Diversity Score				
Low	5.42 ± 0.86	0.05	5.32–5.52	0.030
Medium	5.50 ± 0.92	0.03	5.45–5.56	
High	5.56*± 1.04	0.02	5.52–5.60	
Obesity				
No	5.46 ± 0.95	0.02	5.43–5.50	<0.001
Yes	5.81 ± 1.14	0.04	5.73–5.89	
hs-CRP (mg/L)				
<1	5.44 ± 0.85	0.03	5.40–5.47	<0.001
1–3	5.63[#]± 1.14	0.04	5.56–5.71	
>3–10	5.68[#]± 1.15	0.05	5.59–5.78	
>10	5.79[#]± 1.25	0.11	5.58–6.00	
Smoking				
No	5.53 ± 1.06	0.02	5.49–5.57	0.832
Yes	5.54 ± 0.86	0.02	5.49–5.59	

SD = standard deviation
SEM = standard error of mean
95% CI = 95% confidence interval
*Tukey's post hoc test : significantly different compared with low dietary diversity score group
[#] Tukey's post hoc test : significantly different compared with hs-CRP of <1 mg/L group

Mean of BMI was compared across DDS group (Table 3). There was an increase in BMI along with an increase in the DDS group. BMI in medium and high DDS group was significantly higher than in low DDS group ($p = 0.005$ and <0.001, respectively). This relationship is consistent after adjusted for age, sex and smoking ($p = 0.003$ and <0.001, respectively). These findings confirmed that DDS is positively associated with BMI.

Multivariate analysis showed that DDS, obesity and hs-CRP were associated with HbA1c ($p = 0.030$, $p < 0.001$ and <0.001, respectively). Age and sex also showed a significant association with HbA1c ($p < 0.001$ and <0.001, respectively) whereas smoking was not associated with HbA1c ($p = 0.175$). Age has the strongest association with HbA1c ($\Delta R^2 = 4.44\%$) followed by obesity ($\Delta R^2 = 1.89\%$) (Table 4).

Table 3. Association between dietary diversity score and body mass index

Dietary Diversity Score	Crude		Model 1		Model 2	
	Mean (95% CI)	*p*	Mean (95% CI)	*p*	Mean (95% CI)	*p*
Low	22.48 (22.01–22.96)	Reference	22.51 (22.03–23.00)	Reference	22.60 (22.12–23.07)	Reference
Medium	23.39 (23.12–23.66)	0.005	23.41 (23.16–23.67)	0.001	23.43 (23.18–23.69)	0.003
High	23.74 (23.57–23.90)	<0.001	23.72 (23.56–23.89)	<0.001	23.70 (23.54–23.87)	<0.001

Table 4. Multiple linear regression analysis explaining variance in HbA1c

	HbA1c (n=3,825)				
	Coef	*p*	*β*	R^2 (%)	ΔR^2 (%)
Dietary Diversity Score	0.018	0.030	0.034	0.21	0.21
Obesity	0.266	<0.001	0.107	2.10	1.89
hs-CRP	0.124	<0.001	0.088	2.75	0.65
Sex (male)	0.192	<0.001	0.096	3.18	0.43
Age	0.019	<0.001	0.212	7.62	4.44
Smoking	-0.065	0.175	-0.030	7.66	0.04

Dietary diversity score and age are in continuous data
hs-CRP is in log (hs-CRP + 1) form
Coef = regression coefficient
β = standardized regression coefficient
ΔR^2 = change in R^2 after each variable was included in the model

Discussion

The present study found that HbA1c was higher in participants with a high DDS than in those with a low DDS. Additionally, HbA1c was higher in obese participants than in non-obese participants. Moreover, hs-CRP was correlated with HbA1c. Furthermore, DDS, obesity, and hs-CRP were associated with HbA1c.

The relationship of DDS and impaired glucose metabolism has been studied. Research showed that the higher food diversity as measured by DDS, the lower the tendency to experience glucose regulation disorders (prediabetes and diabetes) as measured by fasting plasma glucose.[28] It was suggested that various foods will increase the consumption of nutrient-dense foods that can provide benefits including cardio-metabolic health.[29] Dietary diversity is a protective factor against metabolic syndrome. It was because high food diversity associated with consumption of healthy food groups such as vegetables, fruit and fiber.[30] In addition, diet diversity can contribute to the reduction of oxidative stress because DDS is positively associated with markers of antioxidants in the blood.[31] Overall higher food diversity is associated with a healthier diet.[32]

There are still limited studies on the relationship between DDS with HbA1c. A study compared the mean DDS in

the glycemic control group based on HbA1c levels in type 2 diabetes patients. Mean DDS in group with HbA1c of <7% was significantly higher than group with HbA1c of ≥8%. This indicated that consuming variety of food might help patients' glycemic control due to dietary diversity increase micronutrient and phytochemical intake.[33] In the other study, there were no significant differences in the mean fasting blood glucose level or 2-hour postprandial glucose across DDS quartiles.[14]

There was a positive association between DDS and HbA1c in present study. HbA1c is a non-enzymatic process product between hemoglobin and glucose when glucose attached to β chain of hemoglobin.[4] HbA1c formation is affected by various factors such as blood glucose,[34] the lifespan of erythrocytes[35] and various clinical conditions.[36]

Most study participants were in the high food diversity group or consumed more than five food subgroups in the last seven days. DDS was measured qualitatively and irrespective to the quantity or gram of food consumed and distribution of nutrient intake, therefore, there were no cut-off points of food portion in the scoring system. Hence, it disregarded the possible threshold point of food portion that actually affects the body metabolism. In addition, limited food items listed on the questionnaire led to DDS measurement to be unable to detect food consumption outside the list.

Unfortunately, studies on the relationship between food diversity or DDS with HbA1c which we can compare our results with are very limited. Therefore, more research is needed for further investigation and better understanding on the association between dietary diversity and HbA1c.

A significant positive relationship between DDS and BMI was observed in present study. Greater DDS was associated with an increase in BMI. Prior studies have reported similar findings in children[37] and adults.[38] Furthermore, a case-control study showed that DDS was associated with obesity in adults.[39] It has been reported that higher DDS was associated with higher energy intake.[17,38] However, other study found that low DDS was associated with overweight and abdominal adiposity in female students aged 18–28 years. The study noted that higher DDS was related to greater consumption of low-energy-dense food such as vegetable and fruit.[40] These inconsistent findings may be due, in part, to the different methods used to measure DDS in studies. To our knowledge, there is a lack of consensus to date about the best method to measure DDS. Accordingly, promoting dietary diversity as a part of healthy diet requires careful consideration. Improving moderation should be emphasized to prevent excessive energy intake.

Other finding in this study is consistent with previous study that obese participants had significantly higher HbA1c levels than those of non-obese counterpart.[41] A different result was found in study involving elderly participants. There was no significant difference in HbA1c levels between obese participants and non-obese participants using the BMI (BMI $\geq$ 30) indicator in determining obesity. However, there were significant differences in HbA1c between the two group when using the International Diabetes Federation criteria for central obesity (abdominal circumference $\geq$94 cm for men and $\geq$80 cm for women).[42]

Obesity has been known to induce glucose regulation impairment. Adipose cells that are enlarged and inflamed trigger an increase in proinflammatory cytokines secretion and on the other hand lead to decreased adiponectin. Other than its role as an anti-inflammatory cytokine, adiponectin also plays a role in glucose regulation, especially as a regulator of insulin sensitivity. In addition, secretion of proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-6 (IL-6) would induce local insulin resistance.[43] Insulin resistance leads to glucose regulation impairment including fasting hyperinsulinemia, fasting and postprandial hyperglycemia, and elevated HbA1c.[44]

This study confirmed that hs-CRP is associated with HbA1c. It is consistent with previous studies.[45] Evidence has shown that CRP is associated with insulin resistance.[46] This study also showed mean differences in HbA1c levels among the four hs-CRP groups. Means

HbA1c in hs-CRP of 1–3 mg/L group, 3–10 mg/L group and >10 mg/L group were significantly higher than in <1 mg/L group. These findings confirmed that inflammation even if it is low-grade is related to glucose regulation.[47] In vivo study suggested that CRP plays a role in insulin resistance in the liver by disrupting the insulin signaling pathway.[48] Other in vivo study has also found that elevated levels of CRP interfere with glucose homeostasis and cause insulin resistance by inhibiting glucose delivery to the skeletal muscle.[49] In present study however, the correlation of hs-CRP and HbA1c is weak, indicated by a small but statistically significant correlation coefficient (r). This might be due to the large sample size. Hence, the clinical significance has not been ascertained.

Multivariate model showed that age and obesity have the strongest association with HbA1c among all other predictors. Study has shown that age is the strongest predictor for HbA1c variance.[34] Consistent findings have been accomplished on relationship between age and increasing HbA1c levels.[50]

This study has several limitations so that the results should be interpreted accordingly. This study is a cross-sectional study in which the measurement of variables was performed only once at one point in time so it cannot describe the temporal relationship among variables. In addition, the limited number of food items in the food frequency questionnaire might cause the inability of measurement to detect the consumption of other food items outside those in the food list. Lastly, other factors that can affect HbA1c to some degree, such as, nutrient intake, diet quality, blood glucose, and other clinical conditions were not examined in present study.

Conclusions

This study confirmed that obesity and hs-CRP are associated with HbA1c in Indonesian adults. DDS was observed to be positively associated with HbA1c and BMI. Thus, promoting dietary diversity requires careful consideration especially in terms of obesity. Furthermore, more researches are needed for further investigation and for better understanding about the association between dietary diversity and HbA1c.

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Conflict of Interest Statement

There were no conflicts of interest in this study.

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